TRANSCRIPT OF PROCEEDINGS

IN THE MATTER OF:)
)
STAKEHOLDERS MEETINGS)
(CHLOROGEN))

Pages: 1 through 48

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IN THE UNITED STATES DEPARTMENT OF AGRICULTURE

IN THE MATTER OF:)
)
STAKEHOLDERS MEETINGS)
(CHLOROGEN))

Training Rooms 1 and 2
4700 River Road
Riverdale, Maryland

Monday,
February 23,2004

The parties met, pursuant to the notice, at 10:15 a.m.

BEFORE: CINDY SMITH, Deputy Administrator
Biotechnology Regulatory Services

ATTENDEES:

For USDA, Animal Plant Health Inspection Service (APHIS) and Biotechnology Regulatory Services (BRS):

REBECCA BECH
JOHN TURNER
SUSAN KOEHLER
NEIL HOFFMAN
JIM WHITE

For Chlorogen:

MELINDA MULESKY
DAVID WILLIAMS
SHARON BERBERICH

Participant:

SHIRLEY INGEBRITSEN

P R O C E E D I N G S

(10:15 a.m.)

MS. SMITH: Well, good morning, and welcome to our stakeholders' discussion series on our upcoming environmental impact statement and revised plan for biotechnology regulations. The purpose of these briefings is to share information regarding our plans to develop an environmental impact statement, an EIS; and amend our plant biotech regulations and to gather diverse and informative input, which will support thoughtful and effective decisionmaking on our part in terms of our new regulation development.

We want to thank you for taking time from your busy schedules to participate in this meeting and to share your thoughts with us. As you likely know, we recently participated in interagency discussions with EPA, FDA and the White House, which concluded an agreement for us to revise our regulations based on the authorities and the Plant Protection Act of 2000.

We also concluded those discussions with general a agreement on how our biotechnology regulatory approach would evolve. Still, there is much opportunity for public stakeholder input as we move forward to more fully flush out the specifics of our regulatory enhancements.

To this end, what we would like to do in these meetings is to have an opportunity to hear your thoughts, as well as have an informal give and take of ideas. We have a unique opportunity to have this kind of discussion because we have not yet moved to formal rulemaking. Our discussion will be professionally transcribed for several reasons. First: an accurate record of the discussion will facilitate our ability to capture and then refer back to your specific input.

Secondly, in the interest of transparency and fairness to all stakeholders, we will be making available as part of the public record and potentially including on our Web site documentation on all of our stakeholder discussions, so that every stakeholder and member of the public will have the benefit of the in-depth discussion that we may have with you today.

Chris Zakarka, in the corner of the room, will also be capturing some of the key things and issues on the flip chart just to help our discussion as we go along.

Of course, I should emphasize that while our plan is to share information on the direction that we are likely to take during this upcoming rule-writing process, what we will be sharing is our thinking here in Biotechnology Regulatory Services. During this

process, the public and stakeholder input will likely influence our thinking and likely cause our thinking to evolve.

In addition, other officials in USDA, including our administrator, undersecretary, our office of general counsel and the secretary, will certainly be expected to provide insight and full direction to us as well. So while we value all input, it is important for us all to recognize that our thinking will likely evolve. So while we may have a very enthusiastic discussion with you or with others on certain aspects of the system, I don't think because we talk about an issue that necessarily ensures that that issue will evolve in the same direction as we have talked about it today in terms of what we see in our regulations.

Finally, since it will be hard to predict what the final regulation will look like, which will emerge from this process, I would like to briefly share with you our overall BRS priority areas of emphasis, which we use to set direction and help guide the development and implementation of regulatory and policy strategies and operations.

We have five areas of emphasis, and I will just run through these very briefly with you.

Rigorous regulation, by this we mean rigorous regulation which thoroughly and appropriately evaluates and ensures safety and is supported by strong compliance and enforcement.

Transparency, by transparency we refer to transparency of the regulatory process and regulatory decisionmaking to stakeholders and the public. We believe transparency, as a process, is critical to building public confidence.

Third, a scientific-based system. It's our goal to ensure diverse and a competent scientific staff, assessing their most current scientific knowledge and state-of-the-art technologies, and ensuring that the best science is used to support regulatory decisionmaking to assure safety. Our fourth area is communication, coordination and collaboration, with a full range of stakeholders.

And finally: international leadership, ensuring that international biotechnology standards are science-based, that we support international regulatory capacity building, and we consider international implications in our policy and regulatory decisions.

With that, I would like to open the floor to hear your comments and discussion. I will ask for you

to start with just an identification of your group and with just a small explanation of your group for particularly the record. Initially, since this is being transcribed to help the transcriber's job, if we could each say our names before we start speaking until we have all spoken enough that the transcriber knows who is here and who is speaking. So with that, I will let you proceed.

MR. WILLIAMS: Thank you. My name is Dave Williams. I am head of operations for Chlorogen. Coming with me today is Sharon Berberich. Sharon had started out with Chlorogen leading our regulatory efforts and currently is heading up our ag business development group. To my left is Melinda Mulesky, who has taken over responsibilities for ag regulatory and field operations.

Since we didn't have an agenda laid out, other than to speak directly to the federal regulation notice on proposed EIS, what I thought I would do, if this is appropriate for this meeting, is to give a very short introduction who Chlorogen is; a little bit on our technology because we think that it is very germane to what you need to look at while you are developing these new regulations; and then a few general comments I think that might be helpful on how

we take an overall view of the USDA; and then get into the proposed regulations.

If that works, okay, we will head in that direction. I also have some handouts that will reflect this agenda and I can hand those out as we get further into it.

Chlorogen, obviously, is a plant transgenic-based company. We look at ourselves as a biopharm company more than an ag company and that is a very important concept to us. My tendency is to use plants as a tool for manufacturing biopharmaceuticals, so maybe that's a little bit different perspective than -- companies who have taken that have been looking more at the agranomic trade, feed-trade opportunities within the ag sector.

Actually, part of our mission statement is that we want to produce proteins and form antibodies for human therapeutics, so that's our ultimate goal. The technical founder of Chlorogen is Dr. Henry Daniell, who is currently at the University of Central Florida. He has been working on this particular technology and the basis of which is intellectual property that he began developing in 1988, so we have well over 10 years of history in developing this technology.

The company has been in existence for about two-and-a-half years, but, more formally, with our ability generate significant funding. We have really been moving forward in a rapid fashion since June of last year. We are headquartered in St. Louis, Missouri, as I guess most of you know. In the handout, we have an address for our Web site, so if there is any further interest in reviewing what Chlorogen is all about, we can refer you to the Web site.

With regard to the technology, we think this technology is very unique, not necessarily to Chlorogen. But in terms of being able to move the technology forward, we think it is very unique because of our very strong intellectual property position and experience in the field of chloroplast transformation. Unlike most of the other transgenic plant technologies, we do not transform in the nucleus. We transform in the chloroplast.

There are a number of criteria that are really specific to chloroplast transformation. We think we have a very high level of containment with chloroplast. In general, genes are inherited maternally, unlike generation through nuclear transformation, so you don't see at least functional

genes showing up in a pollen, so that is a very significant issue on containment. We generate very high levels of protein production, up to 40-percent total soluble protein.

The protein insertion mechanism is very specific. There are no positional effects. We utilize homologous recombination for the insertion of the genetic elements, so we know exactly where they are, exactly how they function as opposed to some of the nuclear transformation where it's a hit-and-miss insertion into the nuclear genome. Probably most important at this point in looking at the history of the development of regulations, at least over the last few years, being in tobacco, we can consider ourselves a nonfood or feed crop, which we think is very important today, certainly in the arena of public perception.

We do not use seeds for any of our processing. We only use whole-leaf tissue. Whole-leaf tissue is harvested and transported. The only time that we produce seeds is for a generation of our seed bank, and that would be done and contained in a greenhouse operation.

So that's the basis for the technology. I did want to keep that part of it very brief. I think

we have some general comments at this point on how we have interacted with the USDA over the last few years. I would like to turn that topic over to Melinda Mulesky.

THE COU: Okay. First of all, I would like to start out with what I consider, in the years of doing the permitting process, to be very positive changes and adoptions by the Agency.

A couple of these I will go through, namely assigning a biotechnologist to each company on a three-year rotation that provided you with a contact person with the Agency, if you have questions, comments. That has been an excellent situation, the comprehensive permit system, the amendment process also. That's one in which you could incorporate changes without having to refile, starting over again with the paperwork from scratch.

The variances, if you could justify that your system, from a biological standpoint, there would be a variance in a certain situation. If you could justify that, you could put those changes in. And, of course, also asking for input from the industry that you are regulating, public comments through the Federal Register system. Those have all been excellent changes.

With that said, I know that after receiving an E-mail from John Cordts, he had mentioned that you were encouraging any areas for improvement. I would just like to highlight a few of those being that I have noticed initially. Let's say when you first file your applications. This has been a sporadic problem where the initial status during that first 30 days, there has sometimes been inconsistencies and notification of the applicant. Again, like I said, that has been a sporadic problem.

More consistently, the areas of improvement that we have witnessed have been in the area of facility inspections, particularly when it is a new facility. Also, as far as improved communication, I think a key issue here is improved communication between the Maryland office and the state and regional officials. In many cases, we have stepped in and actually had to contact individuals ourselves.

So I think in a case like that, maybe that could be simply improved by simply a training program for some of these state and regional individuals, especially if they are newly appointed to the position at the state and regional level. There was some confusion as to what their duties were, or if the state has not had much experience with releasing

genetically-engineered organisms. So maybe possibly again, just simply implementing a manual and training program, maybe inviting the state personnel to this office for particular training.

Again, I also realize that the numbers of permits, the numbers of products, the acreage, the locations have all dramatically improved from the eighties, early nineties, so maybe this is simply a question of additional staffing to address some of these deficiencies. Again, the other aspects, the amendments, I guess one question we would have is I know that you cannot amend to add a new state. Again, that's something open for debate. In our case, we may have particular field release in a state and then skip that state the following year.

The bottom line, I think, here is we would support any regulations to decrease that 120-day turnaround time. From a biological standpoint, that would be our preference. So, essentially, if you could have simply a renewal system, or if you did not make major changes, you had your same recipient organism, maybe you might want to amend to add states. If we could have it just a year-by-year renewal system that would be positive for us.

MS. BERBERICH: I had one more comment, and

this is something that I actually forgot to mention to Melinda and with the experience last year. The coordination between OIG and your group also seems to be not maybe where it needs to be, the coordination between inspections and results. That might be an area of improvement that we forget to add on the list.

MS. MULESKY: Thank you.

MR. WILLIAMS: At this point, as I said, we wanted to keep those comments very brief. I think now we are ready to move into the primary function of this meeting, just to talk about the proposed regulations.

Sharon is going to lead the discussion from our perspective on the new Federal Register notice. Before I turn this over to Sharon, one thing I would like to point out. Relative to my background, more recently, I have been on the plant trench shedding business, but I've spent many, many years in the biopharma business and transitional technologies and GMP operations with the FDA, which is highly regulated environmentally.

From my perspective, I find that those regulations really are critical in being able to function in the role that the FDA wants to see biopharma companies function in. I think that those types of regulations are also welcomed in our efforts

out in the field, even prior to getting into the operation facility. So I m a very strong proponent of having strong regulations in place, certainly regulations that everybody can work with them, but strong regulations nonetheless.

The important thing is that once these regulations are in place, and many times it can be painful getting to the end of the road, people that have spent many years in the GMP operations under the FDA really find that it ss almost impossible to go back to the different, less-regulated system because they find it allows you to be much more effective and efficient in performing your business opportunity.

Again, I think I reflect the view of Chlorogen management in general, that we actually welcome FACA regulation here, and we see that it can do nothing but benefit us in the industry as a whole.

So because of that, I would like to turn this over to Sharon.

MS. BERBERICH: Sharon Berberich. I forgot to say that before. Before I start, I wondered if there's any questions about the technology or what we do at Chlorogen? Because I think it's important for everybody to really understand the technology before we start to talk about our response to the Federal

Register notice. Does everybody understand chloroplast transformation? Very well. Okay. Great.

The first topic we would like to address, or the first question, I think, is really one of whether or not the EIS should be undertaken and the first handout slide that we have in this area, I think -- our position is that we fully support an amendment and the EIS exercise.

We believe that by examining the environmental impact of all these different products that have resulted from advanced biotechnology, that you actually will be able to develop a regulatory system that is more distinct for these types of products and identify gaps that may be in the regulatory framework, not just at USDA but among the agencies. So that's pretty clear that we support the revision.

We believe that, as we go through the environmental impact statement exercise, this idea of safety but at a tiered rate really considering the product type, et cetera, is going to be important. Because the products are so diverse now that I don't think you can just take and prescribe one system for the products, so we really support a risk-based product-by-product tiered system.

So what we have done is try to make our responses generally follow the Federal Register notice. There's a lot of questions in here, and a lot of them have the same answers from our perspective, so we tried to group them as best we could. So in Categories 1 and 2, or Sections 1 and 2 on the Federal Register notice, the first one addresses basically the establishment of these different categories.

I think that we support that effort to actually put different categories, rather than just genetically-engineered organisms. Try to put those in categories where you can establish a framework around each of those categories. So what we understand from the notice is that there would be a category that would be a noxious-weed category. That word kind of scares us all in the GMO area, but that would be those products that really have uncharacterized DNA, or express uncharacterized products, the novel proteins, the novel genes, and the biological control agents.

As well, probably the unapproved FIFRA products, such as insect or herbicide tolerance. You proposed to go there. We are not sure why that thinking is. Maybe you would like some input on that later. Then there might be a category that goes in an assessment of low risk to high risk. That would be

dependent on your product, the hazard, the expressed protein or DNA, the exposure in the environment to that product and any remediation issues that might occur from an inadvertent or exposure in the environment.

Then finally, we agree with a separate category for those products that are not produced for food or feed. That would be the plant-made pharmaceuticals and the plant-made industrials. I think that's a key here that it is not intended for food or feed because that takes you down a whole different regulatory path. Then again, we will just keep coming back to this tiered-risk assessment.

I think this answers all of the questions in Section 2 on the Federal Register notice. The criteria that would be required to establish a risk-based system or an exemption for regulation, I think, is a discussion that would take a lot of time, and we have actually thought about that specifically for our business. We have pages of information about the product type, how many acres we have out there, and how we would follow our tiered-risk assessment for environmental impact.

We can share that with you at another time if you would like. It's also the subject of a USDA

grant that Dave submitted. We've actually gone to the FDA to try to get funding to actually start some of those studies. So again, this theme about the data requirements matching the level of risk to the product we think is very important. It's right along with your initiative; it's science-based.

Just stop me. I will get rolling and I will just keep talking.

MS. KOEHLER: I have a question. When you say PMPs and PMIs should not be exempt, should not be exempt from what?

MS. BERBERICH: We actually agree with the plant-made pharmaceutical and the plant-made industrial industry group, the Blinder (ph) bio, which has made some strong statements about the fact that they should not be exempt from regulation, so they should not be eligible for deregulation. We also support that they should not be approved for food or feed use under CFSAN. So you are exempt from any other requirement, the few that you might put for movement or field release.

Not to say that as you get into the process, like Dave talked about, where you get to a mature process where you have characterized everything from A to Z, then the regulation might be relaxed or

standardized. But, for now, regulatory oversight is not important for these products.

MS. KOEHLER: Thanks.

MS. BERBERICH: Sure. If we move into some of the topics that are covered in No. 3 and 4 of the Federal Register notice, again we get to this notion of tiered risk-based criteria, and actually, we are going to present some of the things that we have thought about that are critical, so these are high-level criteria. But, of course, No. 1 on the list is always the risk for gene escape, whether it's through pollen, seed, wild relative, or compatibility with a wild species.

Again, if we talked about Chlorogen's business, one of the reasons that this company is so exciting is the fact that we have our genes in the chloroplast and that there's literally almost a zero risk for escape through pollen of the gene, even to tobacco, non-PMP tobacco. Of the states that we intend to produce in and where tobacco is typically grown, there's no wild relatives, and the idea that we will use, as our starting material, the vegetative portion of the plant rather than the seed means that we don't have to transport large amounts of seed through states, and that also lowers the risk.

Then the other consideration is the potential for contamination of our food supply by these products that the food are known to crop and there is very little risk that tobacco is going to get into the food strain. It's non-food crop. On a scale compared to corn, there's very few acres that have actually being grown for smoking tobacco, if you look at that.

MS. INGEBRITSEN: Okay. For plant-made --

MS. BERBERICH: For plant-made pharmaceutical production, or for tobacco, or for smoking?

MS. INGEBRITSEN: No, no, no. I'm sorry. What you are doing.

MS. BERBERICH: Okay. What we are doing. Actually, yes, and I can give you a comparison from my experience and from Dave and Melinda's experience. If you get a nuclear transformation and your expression level is relatively low, it's below one gram per kilogram, you need hundreds of acres to produce what the typical pharmaceutical need, which is about 600 kilograms of protein. You need hundreds of acres, probably around 120.

For corn, you would need a minimum of a 1,000 acres to produce that same amount of

pharmaceutical material. But in our system, we have really high levels of expression, around two grams per kilogram, and we would only need tens of acres.

MS. SMITH: Shirley, could I ask you to state your name and repeat your question loud enough. If you are not at the microphones, the transcriber can't hear you.

MS. INGEBRITSEN: Should I do it again?

MS. SMITH: No, no, no, that's fine. If you are going to ask a question from here, just make sure you state your name and speak loud enough so she can hear you.

MS. INGEBRITSEN: I am Shirley Ingebritsen and I am with BRS staff. I asked for clarification of a typical number of acres that Chlorogen would be likely to need to produce one of its products.

MS. SMITH: Thanks, Shirley.

MS. BERBERICH: So 10 to 20 acres would be all that we would need to produce that level of pharmaceutical protein. The other issue that we think -- our criteria would be the stability of the transformation system. We know that in tobacco there are some transient systems that are used. Some crops are notorious for jumping genes or losing the expression of the system, but the chloroplast system

is extremely durable. It uses nature's science to actually create a homologous product.

There's no history of gene silencing, nor is there any history that's been documented. And it has been scientifically backed that the chloroplast genes actually escape into the nucleus. Actually, Chlorogen is planning on doing some modeling to show what the statistics are around that, if it should happen, but it's never been documented.

MS. MULESKY: Sharon, if I might also point out: When you have nuclear transformation, it's nontargeted, so it's randomly junctioned to the chromosome of the organism. This is highly specific. Homologous reformation is highly specifically targeted to the same site.

MS. BERBERICH: So it doesn't integrate unless it's in the right place, because it has to have both sides of the gene sort of together at the right place.

MS. MULESKY: The other criteria for risk-based assessment, I think, is the exposure profile. This is pretty standard to find out: what the expression is, what tissues, what organisms are exposed? If we talk about our system because it is green tissue, the highest expression is in the leaf

tissue, and that's the material that we take out of the field.

So we have relatively smaller amounts of tissue to be incorporated back into the field, and we're taking most of it off OF the field. In the leaf tissue, because the nature of tobacco, is not really something that a lot of nontargeted organisms want to eat. The earthworms don't even go around tobacco. So we think that that actually gives an advantage for our system. There's also no exposure to beneficial insects that would feed on pollen for nectar.

Our system doesn't allow the plants to go to flower, because the expression drops off or we don't get as much leaf tissue. So, actually, our harvesting system would take the plants out before there's any flowering or seeds or pollen even made.

Then we talked about the overall small acreage of the system. Then, of course, the function and the safety of the expressed protein has always got to be considered. That's usually at the top of the list, but we put it at the bottom because it's so obvious. We think there that there's two important things. Because most of the proteins, that are going to be expressed in these plants, actually already have a history of safety. Many of them have already been

through the FDA at some level, for a new drug or some clinical trial, that the safety to humans is pretty well known, except for the exposure: the dermal or oral exposure activity of the protein should be examined; and then how persistent it is in nature?

Many of these really haven't ever gotten out into the environment. They're in manufactured and contained facilities that the protein in the environment ought to be looked at.

MR. WILLIAMS: If I could?

MS. BERBERICH: Yes.

MR. WILLIAMS: The vast majority of proteins that would be looked at for therapeutic value, those particular families of proteins, really a great deal is known about those. The vast, vast majority of these proteins have no oral activity involved. They have to be gradually administered, injected, they only act systemically in the circulatory system of the human patients. So we think that's a very important point in terms of assigning risk to that particular protein.

MS. BERBERICH: In fact, the protocols that are used for food safety assessment, the digestive fate analyses and the allergen and toxin homology searches, the ILSI Group has actually standardized

those process and validated some of those systems. That might be the first tier. If you pass that, then you may not need to do oral toxicity or oral activity studies for some of these proteins.

Any other questions?

So as we go to No. 5 and 6 in the Federal Register Notice, we are going to make some statements about that. The notion of regulating the product within the tissue, which would extend the USDA jurisdiction to nonviable tissue, which is a little bit out of what we are used to, a little bit different. Our view is that the product is regulated by the FDA; and, in the case of a herbicide or fungicide, regulated by EPA.

So, we would actually like to maybe have a discussion about those after we run through the rest of these to understand your thinking about regulating nonviable tissue. This No. 5 is the smallest. It has the smallest amount of spaces of statement in the Federal Register notice, but it's probably one of the issues that jumped out at us the most.

We talked about the second bullet, that we are in line with the industry group and that we believe that these products, that are not intended for food or feed, should not be deregulated. We support

the risk-based approval process, actually a separate process that PMP and PMIs, a new process. What that would look like would be interesting to have a discussion about, but we support that.

This is kind of redundant here. Regulations and permit requirements should be risk-based and distinct. We talked about that. That's important. The safety of the host system we think is probably another consideration for the pharmaceutical plant-made industry, and the specific risk of the product.

So once again, we would like to have a little clearer understanding of what the category of noxious weed would cover and would PMIs or PMPs potentially fall into that category? How would that influence the regulation?

Anything to add to that?

Then the last 7 through 11, there's a few of the points here that really don't pertain to pharmaceuticals that are plant-made, so we're not going to address those. But the ones that do, we have grouped them all into a category. There was a question in the notice about adventitious presence and food safety and how USDA ought to consider putting in place guidelines for that. For crops that are low risk that are not PMPs or PMIs, I think that's a very

good thing to consider.

We are not going to address those criteria here because that's not our business. But for products, again, that are not intended for food or feed, we would prefer to keep those out of the food chain and not see adventitious presence, I guess, approved by the USDA. If it turns out that that would be the case and that there would be some low level that's tolerated, then it has to be driven by the safety and we believe should be backed by some level of food-safety data similar to what you would have to submit to get a product approved under CFSAN.

MR. WILLIAMS: Dave Williams again. Just one comment on that. I think that position may seem a little bit selfish for a company that's not producing a food or feed product. But our position, as being a member of the PMP/PMI industry group as a whole, we tend to get lumped in with everything that happens to the industry. So we want to make sure that if there are issues with food feed crops not intended for food or feed, that there's enough regulation there and enough control that the impact of this regulation or the impact of having some adverse event occur does not impact us just because we are associated as being a PMP company.

MS. BERBERICH: The one area that we think there could be some changes, based on the risk or the established safety of the system or the plant, would be in the area of interstate movement. Based on the risk of environmental impact or escape, maybe those regulations could be relaxed as the system matures. In fact, for PMPs and for crops that are not PMPs or PMIs actually support that effort.

Now, thinking down the road about how the USDA regulations mature as you get a product closer to market in the PMP industry, we actually believe that it would be advantageous for USDA to develop a system similar to what the FDA has established in the master drug file, that it be process driven. Rather than regulating the product, you regulate the process. Because, at a certain point, the regulation of the product becomes an FDA issue and the production of that product in the field really becomes an USDA issue.

So it's a little bit different thinking to be regulating a process rather than a product. That is where we would like to see it go and maybe have some discussion after I finish speaking about that.

The proposal to change the container requirements to performance-based versus prescriptive

is very much supported by our business and I think by the industry to make that part of the permit-approval process. So before you apply for an interstate movement permit or a release permit to actually have your container described, how you are going to move it and have the performance specifications of that container in place and have that as part of the approval process, we think it is going to save someone here at the USDA a lot of paperwork on variances.

We have several other comments to the Federal Register notice, which we will submit in writing as a formal statement. But the key things that we would like to summarize that are specific to our business: We believe that PMP production in tobacco has a low-risk profile, especially with the chloroplast transformation; we support a change to the regulations, as long as it is risk-based and a tiered approach that would bring in data requirements as you go through a process to evaluate those criteria.

We fully support the preparation of an environmental impact statement by the USDA and believe that we can help and the industry can help, and we are very pleased that you are having these stakeholder meetings up front. We would like to continue the conversation and input with you as we go through that

process. We just supported distinct regulations for products that are not intended for food or feed, and we would like to understand more about the noxious-weed proposal.

With that, I will conclude and ask if Dave or Melinda have any other comments to add?

MR. WILLIAMS: I think with the next-to-the-last point about distinct regulations, based on risk assessment, even within the PMPs or PMIs, they are obviously going to be distinct difference in risk, as Sharon has already pointed out. In our case, we are using chloroplast transformation processing that is distinctly different in technology from nuclear-transformed material. Even if it's from nuclear-transformed tobacco to chloroplast-transformed tobacco.

Then obviously, you have those differences between the production system that uses green biomass, green-leaf tissue, versus C-production systems. So it seems readily apparent that we truly need some sort of tiered evaluation of risk. I think today everybody's been pretty much caught up, lumped into a single entity, so if there's, I guess, a takeaway message at all we hope we get across here is that tiered regulation risk-based, regulatory market.

MS. SMITH: I would like to echo what Dave said. The appearance to me is that the highest risk has been applied generally across the category of PMPs or PMIs, rather than the distinctions.

MR. WILLIAMS: I guess the last slide that we have here was just a talking bullet. What I would kind of like to ask is: As we read the Federal Register notice, there are two pages of rhetoric here. You don't really get the best sense of what the management thinking is within the USDA, so we thought we would like to turn the tables around here and pose that question to you and get a little more feedback regarding: What do you think of the strategic future of certain PMPs or PMIs, where that is really headed? That will help us, I think, in trying to define what we would like to see.

That goes back to your point, Cindy, about communication. One of your very important points was the communication issue. Again, it's easy for me to say this coming from a FDA-regulated industry, but you really have to develop a partnership, or life gets really difficult to move your business forward. I have worked in companies where there had been an adversarial environment between the regulatory groups and the company; and I have also worked in an

environment where it really was a true partnership with the company and they worked hand-in-hand with the FDA.

The ultimate goal was to get a particular product on the market, and I see that there is no difference here. Once that partnership was developed, things really worked well and usually there is a very positive outcome as a result of that. So again, if this fits within the intent of this meeting, we would like to hear a little bit back from the USDA's perspective, a little bit more than what's being --

MS. SMITH: All right. What I might say -- first, let me thank you for your thoughtful comments. We appreciate you both acknowledging working well as far helping us identify opportunities for improvement, in addition to our discussion on the Federal Register notice. Specifically, I want to just share a couple of general thoughts in terms of teaching how-- I think in your terms of regulating pharmaceuticals and industrials, one thing we are thinking about, and, of course, it will evolve obviously through this public process.

Right now, we are looking at two avenues to regulate pharmaceuticals and industrials, particularly in terms as they approach and go through the

commercialization. As you know, we have a system now where if certain safety criteria are met, there is the process with deregulation. So, of course, one of the questions for us in the new regulation, where we will find the pharmaceuticals and industrials stand within that context. What we are looking at are two avenues, one avenue of what kind of criteria pharmaceuticals and industrials would have to meet, in order to be approved to move out of our regulatory system, comparable to deregulation.

But the other area that we really would want the opportunity to dialogue as really partners; this is a real opportunity, I think, for partnership: is to look at what kind of alternative additional system we can put in place, a mechanism for pharmaceuticals and industrials to be commercialized and you move on to your product-extraction phase while still under regulation. So the question becomes: How do we make that a system that it would be more effective than potentially what might be in place or some other alternative?

A couple of key things we want to consider in that and we would welcome your thoughts on -- I think a very important piece of that is going to be transparency, that we struggle with now. I think the

system can be limited at times now with confidential business information. Pharmaceutical and industrial manufacturing through plants is something that we are going to have to be able to share good information with the public and with stakeholders about.

So can we look at some mechanism without compromising confidential business information? But some mechanisms share more information with the public, in terms of this mechanism for growing pharmaceuticals and industrials under regulation.

I think another obvious area is a way to consider the reality that what we are going to be looking at here is probably some longer-term need to do field tests, in order to obtain what you are growing the product for over a number of years. So you may have the same essential field tests that you want to run for five years straight, and that would suggest that we need a more efficient mechanism, both for you to give us that information, that long-term plan, and for us to be able to respond to that, rather than a fresh process each year on both of our parts.

So that is two of the areas that I think are probably ripe for us to really talk about. We would like to see what kinds of creative options we can come up with, and we can hear from others in terms of that

kind of regulation. So I will stop there and see if you want to share thoughts on that, or if you want to ask some more questions?

MR. WILLIAMS: Generally with pharmaceutical companies, it is actually to our advantage to be as public as we can about products that we are developing, because it enhances our business opportunities out there, mainly because the products that we are making are so high profile and they really impact the general public more publicly than, I guess, you would say with some other ag-related opportunities regarding them producing products that say people want.

So I think you will see that with most pharmaceutical companies out there. Once they come up with a product that they think they can take to commercialization, they want to wave a flag up there and they want to tell people that we have got this great product coming down. Of course, it is all driven by money, and it advances our pretending to raise money or profit from this product.

Obviously, I can't totally speak for the company now without having sign-off from all the way up probably to the board of directors, but I have no problems being a little transparent as long as --

generally, we are not going to release any information that will compromise our intellectual-property position or competitive position.

So many people know what we are doing in a reasonable generic way. I don't think we would have a problem with it, so if there is some way that we could work together and generate a program that would truly increase the transparency beyond where we are right now, we certainly would be willing to work with the Agency on it.

MS. MULESKY: I agree.

MR. WILLIAMS: On your second major point, the second issue about determining to provide an opportunity to look at -- to have our operations without going through a year-to-year adjustment. I think that really is basically what we are interested in there. I think what we have expressed an approach similar to -- my favorite analogy is the drug master file, some sort of compliance agreement where we are able to structure something that let's us, again based on that particular risk, let's us go out in the field and streamlines the process we have right now.

MR. HOFFMAN: I would like to ask a question about when you think is the appropriate time for us to consider your risk analysis? We are in a situation

where we sometimes have a testing phase, a testing phase for products where this very small acreage of a test and then there is progressive testing and the size of the scale gets a little bit larger. But in this discussion of whether or not we would continue to allow commercialization under regulations, at what point, from your point of view, do you see a need for us to consider the full-risk assessment of your product?

Will it be at that very first test where you may be just .01 acres? This addresses the comment that's up there, this 120-day turnaround and this five-year renewal. Because at one point, we need more time than 120 days to consider the full range of effects. Especially as you are increasing the size, there is going to be more potential for environmental impact.

But at what point, in this process, do you see us doing a large-scale consideration for all the risks? At the very beginning, or is it at some phase in between?

MR. WILLIAMS: I can start with an answer to your question, and everyone can chime in if they feel a need to. Let me go back and again draw on my experiences in the more traditional pharmaceutical

areas. Twenty years ago, it was a requirement by U.S. Code that, prior to licensing a product, an environmental assessment had to be done on the product.

Today, because we have the benefit of a lot of years of experience, that regulation has been changed to the point that no EA is required unless there is some unusual circumstances that warrant it. That is a pretty broad statement, but that is basically how it's verbalized in the regulations.

So what the industry 20 years ago tended to do was, under a small-scale operation, they allowed the production of materials; and that allowed the company to generate data up to the point where they wanted to commercialize this product and file for a biological license application or a new drug application.

At that point, that is when the EA requirement kicked in. Again, it was to give the company the opportunity to develop information that they could put into the EA. It also allowed the company, over the period of a few years, because it has given them -- it probably takes a minimum of three years to get to a commercial product, just because of going through the review process by the FDA. More

likely, it is somewhere around seven years or longer before you get that approved.

So that gives you some time to generate the early data. What went along with that is the fact that you are not required to put a significant amount of capital in a virtual period of time determining that information, where that really actually becomes an aside project that I think costs a significant amount of money.

By allowing us to generate that information as we go through the development process, I think your ability to take it slowly, look at the data that are generated and digest that information, you have a little more opportunity to maybe take a different direction and to see some data that may point you to a different direction.

Again, I think it is much more effective if you can move that slowly through the development process. Other than just saying, okay, you need to generate a full package before we could ever let you out in the field. It is going to be difficult for most companies except maybe some of the largest ones. Even then, having to define, really not knowing what your system is 100 percent going to look like, what you need to do is going to be difficult, I think.

So I guess where I am going with this is that my position would be: Under the permitting process, let us develop that information up to a point where we think we are going to take that to commercialization.

MR. HOFFMAN: What is the trigger from when you take it to commercialization? In your own mind, is there a specific process that you have with the FDA? How do we know? We have situations where companies will say, and for purposes of generating revenue, that they are commercializing. In one case they are saying that they are commercializing when, in another, maybe they are not really commercializing.

MR. WILLIAMS: For PMP, certainly, I think one of the new drug applications or biological applications as far -- although I'm not sure how it's going to work out now, since the Center for Biologics has moved into the Center for Drugs. That is a big issue.

As soon as that application is made, even way back when in the drug industry, that is what triggered the EA, and there should be sufficient time. You are looking usually at a minimum of 9 months to 14 months before you get to the end of that review period.

So, again, if you are given time to put that data together, I think that 9-to-14 months gives you ample opportunity to put it together as a full package and submit it to your Agency.

MS. SMITH: We are going to have to wrap up here before too long, so I just want to make sure we move on to any other significant things we have not covered yet that you want to make sure that we do.

MS. BERBERICH: I didn't know if you could comment on the noxious-weeds data and how that fits in with either the categories and regulations?

MS. SMITH: I am not sure if you have seen the definition for a noxious weed.

MS. BERBERICH: Okay.

MS. SMITH: So essentially, what we see is, using that definition to give us the authority to evaluate anything that comes before us for a variety of factors. My guess is that most of what we regulate would not be noxious weeds. But given the potential, it's more a question of: Do we want to take advantage of the authority to consider whether anything that comes from a forest or could come from a forest has the potential to be a noxious weed?

That gives us the ability to evaluate a number of factors and then come to the conclusion that

it either is or is not. But that allows us to have a much more inclusive evaluation process in looking at a number of aspects related to anything that comes before us.

MR. TURNER: In that way, it would be part of our authority under which we operate but not a separate category. If you had asked for a -- or who controlled this group?

MS. BERBERICH: It wouldn't necessarily. Automatically, there wouldn't be a group assigned to noxious weed, and that's not as clear, maybe, in the Federal Register notices as it might be in your mind.

MR. WILLIAMS: Actually, I think for several years now, the feeling from the PMP-industry group was that, under the Plant Protection Act, the USDA probably already had the ability to do that. So I am assuming that they are just really solidifying their position and making it clear to everybody that that is what you want to do.

Secondly, with regard to -- I want to go back to the communication side again.

I think, as I mentioned to Neil as we were talking earlier, I know you folks must be getting overwhelmed. There are a lot of public issues that are pressing right now. I get a little feedback from

the folks that I know here now with regard to the political pressure that also you must be dealing with right now.

Also, with all my years of experience with the FDA, there's never enough staff. There's never enough money. It's difficult. Everybody struggles.

But we certainly have encountered -- as you are going through some growing pains in reorganization here in trying to meet the needs that have been expressed to you. We found that there has been some communication breakdown. We want to do whatever we can to help out that process. I guess we are certainly available at any time to have discussions with the Agency.

Obviously, you are restricted by resources and they have to structure your operations in the way that you are able to. So I don't know that I can make any concrete suggestions with regard to how we can improve that, other than it is a big issue, of course, right now.

Otherwise, it's just going to be -- I don't like using the word painful about the process, but I have done that a lot. So we are open to any suggestions on how to improve that communication.

MS. SMITH: Dave, do you want to be more

specific in what you mean by communication breakdown?

MR. WILLIAMS: Well, I know there were some reorganizations occurring. Actually, maybe I should let Melinda -- because most of these impacted Melinda most recently. But from just trying to contact our biotechnologist and getting some feedback, I think we are on our third biotechnologist in the last year; and we understand that there's a reorganization going on, which sounds like there has been some information that's been passed to us that the people in the permitting area were not even aware of some of the issues that were impacting us.

So I think there are probably some communication gaps even within your Agency, information that isn't being passed on in a timely manner. Let me go back to a really good example. We had submitted a movement permit for the 2004 growing season. We were just in the middle, starting to get a review on that when Cindy's letter came out about the DAC wanting more information to help with assessment of environmental issues. So the review of the permit came to a screeching halt, and we were able to put more information together and again submit it.

During that process, it became very difficult, as we saw reorganization occurring, to get

feedback from the biotechnologist side. At one point, we didn't even know who our biotechnologist was. We thought we knew who it was, and it turns out it wasn't. That change had been made several weeks earlier, which is why we didn't get any response from whom we thought we should be getting responses from.

So we do understand a little bit of what you are going through. It's not an angry criticism. It is just a perspective that we understand that communication is the key to most everything in this business.

I don't know if you have anything else to add to that.

MS. MULESKY: I don't know if maybe at some point during that 120-day period, maybe again personnel issues, so many tasks being imposed on biotechnologists. If maybe they could provide interim reports of the status of where that application is during that 120-day process; and even if there is any way that the applicants themselves can assist with the process, the communication?

In one case, we had a situation where I actually contacted a state official. It had been sitting on his desk; he actually wasn't sure what his responsibilities were. Once I explained that to him,

it had been sitting there for four weeks. This was in 2002. He just filed it under -- he assumed he was only supposed to receive a copy, that he wasn't supposed to give written or verbal approval.

Once he found that out, it was a matter of 24 hours and it was approved. In any way that we can assist in this would be beneficial.

MS. SMITH: Thanks for that clarification, Ms. Mulesky.

Okay. We are going to have to wrap up. Do you have a final question or comment?

MR. WILLIAMS: Just a final comment. We really appreciate the opportunity to meet with everyone here. We have actually been talking internally about doing this, trying to manage in some way to get everybody together and just have a very informal discussion about what we were feeling getting done -- to your agency.

So when the formal opportunity came up to present to the group -- and it's amazing that you were able to get as many people together in one room as this, again it is pretty amazing, considering we think we know how busy you are right now. So again we would just like to express our thanks for having the opportunity to do this.

MS. SMITH: You are welcome. We really appreciate you coming in, and we are very busy, but we also consider this very important. We really look forward to taking advantage of the information that you shared today and continuing to talk with you in the coming months.

MR. WILLIAMS: Well, thank you very much.

MS. BERBERICH: Thank you.

MS. SMITH: That concludes our session. Thank you.

(Whereupon, at 11:25 a.m., the meeting was concluded.)

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REPORTER'S CERTIFICATE

TITLE: Stakeholders Meetings (Chlorogen)

DATE: February 23, 2004

LOCATION: Riverdale, Maryland

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the meeting in the above matter before the United States Department of Agriculture.

Date: February 23, 2004

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